

PENICILLIN RESISTANCE IN GONORRHOEA*

BY

A. J. KING

Whitechapel Clinic, The London Hospital

The incidence of gonorrhoea in Great Britain reached its peak in 1946, one year after the second World War had ended. Thereafter it declined sharply and continued to do so until 1955, when for the first time since the war the Annual Report of the Chief Medical Officer of the Ministry of Health (1957) indicated an increase in the number of patients with gonorrhoea attending the clinics. The rise in incidence has continued and has accelerated (King, 1958). It seems that several factors have been responsible for this increase, but possibly the most important is the emergence of strains of gonococci which are relatively resistant to penicillin. Curtis and Wilkinson (1958) noticed, at the end of 1956, that a small proportion of men with uncomplicated gonococcal urethritis, who attended a large clinic for venereal diseases in London, failed to respond to routine treatment of 300,000 units procaine penicillin given intramuscularly, and that the urethral discharge continued to show gonococci. In some of these cases further treatment with larger doses of penicillin was equally unsuccessful. Between November, 1956, and December, 1957, these authors saw 1,267 cases of gonorrhoea in men, of whom 1,116 were treated with penicillin in routine dosage. Of these 1,116, 124 continued to show gonococci in the urethral discharge after treatment. Curtis and Wilkinson measured the sensitivity of 302 strains of these organisms before treatment was given. They used tube-sensitivity tests which proved to be more accurate than plate tests. Of these strains 19.5 per cent. were sensitive to penicillin at levels of 0.125 to 0.5 units per ml. The failure of treatment after the injection of 300,000 units procaine penicillin in watery suspension, or procaine penicillin in oily suspension with 2 per cent. aluminium monostearate, occurred, for the most part, with those relatively insensitive gonococci; in no case did failure occur when the sensitivity was below 0.03 units per ml.

These significant findings were confirmed by Cradock-Watson, Shooter and Nicol (1958) who tested 200 strains of gonococci and found that 38 of them needed 0.128 units or more of penicillin per ml. for inhibition, and that patients infected with these strains were five times more prone to relapse after treatment than those infected with more sensitive strains.

It appears that this problem is not limited to London. Alergant (1958), writing from Liverpool, stated that, in a recent series of 46 men suffering from acute gonorrhoea treated with single injections of 300,000 units penicillin in oily suspension with 2 per cent. aluminium monostearate, seven failed to respond and gonococci persisted in the urethral discharge after treatment. In these cases, the sensitivity of the gonococci was not measured, but the findings were thought to be significant when compared with a report from the same centre some years earlier (Alergant, 1953) when no failures were reported from the same treatment in a larger series of cases.

To meet the problem arising from increased resistance to penicillin, Cradock-Watson and others (1958) increased the routine dosage of procaine penicillin for treatment of gonorrhoea from 300,000 to 600,000 units. Curtis and Wilkinson also recommended increases in dosage from 300,000 units procaine penicillin in watery suspension to 600,000 or 1,200,000 units, but they believed that an effort should be made to devise a preparation of penicillin which would give a blood-level of not less than 1 unit per ml. for not less than 24 hrs—though preferably for not much longer, owing to the risk that long-lasting low levels of penicillin might produce more resistant strains of gonococci or symptom-free carriers.

It seems unlikely that these measures will provide more than a temporary solution to this problem. The matter is one which calls urgently for study of the gonococcus and its susceptibilities. This organism is susceptible to many other antibiotics, but the cost of most of them is likely to be prohibitive for the treatment of so prevalent a disease.

The evidence as to the existence of penicillin-resistance as a problem in the control of gonococcal infection has been criticised recently by Carpenter (1959). He believes that the evidence of the existence of penicillin-resistant strains, to be accepted, must be substantiated by the following criteria:

- (1) Cultivation and identification of the organism *in vitro*.
- (2) Elimination of the possibility of re-infection.
- (3) Confirmation that adequate blood levels have been achieved.
- (4) Exclusion of the possibly antagonistic effect of penicillinase-type activity by concomitant organisms.

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- (5) Assurance that deterioration of the drug has not occurred.
- (6) *In vitro* demonstration of enhanced penicillin-resistance of the suspected strain.

These criteria are so stringent that they are seldom likely to be fulfilled in practice, except perhaps in a closed community like a prison where re-infection could be almost completely ruled out. Carpenter does not refer to the work of Curtis and Wilkinson in which his criteria 1, 3, and 6 are fully met. As regards point 2, it is never possible to exclude re-infection during the treatment of out-patients, but it seems a fair assumption that when a certain number of patients treated by methods which have been adequate in the past show no diminution of urethral discharge and continue to show gonococci in the secretions, something more than re-infection is responsible for such an unusual development. As regards point 4, there is at present no evidence that concomitant organisms in the urethra are capable of producing penicillinase in sufficient quantity to inhibit the action of penicillin on the gonococcus. The analogy with *E. coli* in gonorrhoeal proctitis requires substantiation by experimental work. As regards point 5, the remedies employed were standard products which showed no evidence of deterioration in their effects upon normally sensitive gonococci or other organisms. Carpenter also refers to the possibility that the gonococcus may invert to an L-phase resembling organisms of the pleuropneumonia-like group, resistant to penicillin. This is no more than a speculative suggestion with no real evidence to back it. Nobody has yet succeeded in converting a gonococcus into a stable L-phase. Finally, he suggests the possibility that previous treatment with penicillin may result in "immunologic antagonism" to the therapeutic agent, but gives no evidence to support this suggestion.

The most valuable feature of this paper is the stress which Carpenter lays on the importance of proper bacteriological control of the diagnosis and treatment of gonorrhoea, the standard of which often leaves much to be desired. Some of the division of opinion which his article indicates arises from the use of the term "resistant". Ideally, this should be restricted to the case in which an organism can be inhibited only by a concentration of an antibiotic which cannot be obtained and maintained in the blood and tissues. This has occurred with streptomycin-resistant gonococci, but penicillin "resistant" strains would be more accurately described as "insensitive" or "partially resistant".

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Résistance à la pénicilline au cours de la blennorrhagie.

Résumé

L'auteur considère que, parmi plusieurs facteurs responsables de la fréquence de plus en plus grande de la blennorrhagie en Grande Bretagne depuis 1955, l'émergence des souches de gonocoque partiellement résistantes à la pénicilline en est probablement le plus important. Il passe en revue les preuves d'existence de telles souches, preuves provenant de deux cliniques de Londres et d'une de Liverpool.

Il décrit les mesures immédiates recommandées pour résoudre ce problème: l'augmentation de la dose habituelle de procaine-pénicilline de 300.000 unités à 600.000 ou 1.200.000 unités. Pour l'avenir, il souscrit à l'opinion de Curtis et Wilkinson (1958), qu'on devrait préparer une forme de pénicilline qui donnerait un taux sanguin d'au moins une unité par millilitre pendant au moins 24 heures et, préférablement, non pas pour un temps beaucoup plus long, car des taux bas persistants de pénicilline pourraient produire plus de souches résistantes de gonocoque ou des porteurs asymptomatiques. Il croit que ces mesures n'offrent qu'une solution temporaire et considère qu'il est urgent d'étudier de nouveau le gonocoque et ses susceptibilités.

L'importance du problème de la résistance à la pénicilline dans la lutte contre l'infection gonococcique est défendue contre la critique de Carpenter (1959). Celui-ci demande, parmi d'autres critères, l'élimination de la possibilité d'une re-infection. L'auteur croit qu'un tel critère ne pourrait être assuré que dans des circonstances artificielles, telles qu'une communauté isolée ou une prison. On ne peut jamais exclure une re-infection lorsqu'on traite des malades extérieurs, mais on peut bien présumer que lorsqu'un certain nombre de malades, traités par des méthodes jugées autrefois suffisantes, continue à avoir un écoulement contenant des gonocoques, et lorsqu'un grand nombre de souches venant de tels cas accuse *in vitro* une résistance à la pénicilline augmentée, la re-infection seule ne suffit pas pour expliquer ces événements extraordinaires. L'auteur approuve l'insistance de Carpenter sur l'importance diagnostique et thérapeutique d'une bonne surveillance bactériologique dont la qualité, croit-il, souvent laisse beaucoup à désirer. Certaines différences d'opinion récentes sont attribuées à l'emploi de l'expression "résistant"; ce terme doit être limité aux cas où l'organisme peut être inhibé seulement par une concentration d'un antibiotique que l'on peut obtenir et maintenir dans le sang ou le tissu. Cela s'applique aux gonocoques résistant à la streptomycine, mais les souches "résistantes" à la pénicilline seraient plus exactement décrites comme "insensibles" ou "partiellement résistantes".